REMARKS

After this amendment, claims 1-15, 40, 41, and 42 are pending. Claims 16-39 are canceled without prejudice as directed to withdrawn, non-elected subject matter. Claims 1, 40 and 41 are amended to clarify the invention, by incorporating appropriate Markush group language and amending Claim 40 to clarify that it is a composition of matter claim, not a process claim. New claim 42 is supported by original claim 41 and throughout the specification. No new matter is introduced by this amendment.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made". Also attached is a clean copy of the claims which is appropriately captioned.

Rejection Under 35 USC §101

> Claim 40 is rejected under this section as directed to non-statutory subject matter. The examiner states that it is a process claims which does not set forth any steps.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons. Claim 40 was never intended to be a process claim; it defines a composition of matter comprising IL-12 and a nitric oxide inhibiting and/or neutralizing agent in a pharmaceutically acceptable carrier. This compositions *may* be used with a vaccine antigen. To clarify this issue, Applicants have removed the language "suitable for use with a vaccine antigen". In view of this amendment, this rejection is rendered moot and may be properly withdrawn.

Rejections Under 35 USC §112, second paragraph

> Claims 1-15, 40 and 41 are rejected as being indefinite. Specifically, claims 1, 40 and 41 and their dependent claims are rejected for the claim language "nitric oxide inhibiting and/or neutralizing agent". Claim 40 is rejected for the language "suitable for use with a vaccine antigen".

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims. Method claim 1, and composition of matter claims 40 and 41 have been amended to incorporate appropriate Markush group language and eliminate the "and/or". The removal of the "suitable for use..." language removed from claim 40 is believed to also comply with this rejection. New claim 42 is added to include the examiner's suggestion for a method step covering a method for making the composition of claim 40. In view of these amendments, this rejection is rendered moot and may be properly withdrawn.

Rejection under 35 USC §103(a)

Claims 1-15, 40 and 41 are rejected as obvious in view of the combination of US Patent No. 5,723,127 (Scott) and K. Fecho *et al*, **1994** J. Immunol., 152:5845 (Fecho). The examiner cites Scott as referring to a method of making pharmaceutical vaccine compositions by combining an antigen with IL-12. The examiner cites Fecho as referring to the fact that macrophage-derived nitric oxide (NO) is involved in depressed ConA responsiveness of splenic lymphocytes, and that inclusion of NO synthase inhibitors restores ConA responsiveness.

The examiner concludes that it would be obvious to remove NO produced by adherent cells from the vicinity of IL-12 action to obtain the immuno-stimulatory and adjuvanting effect of IL-12. The examiner concludes that co-administration of IL-12, vaccine antigen and NO inhibitors would be obvious while screening the immunostimulatory effect of IL-12 to any vaccine antigen. The examiner states that it would be obvious to replace bacterial, viral or fungal antigens with tumor cell surface antigens, as taught by Scott.

Applicants respectfully traverse the examiner's rejection and request reconsideration and withdrawal of this rejection for the following reasons. The combination of Scott and Fecho does not suggest the present invention.

As admitted by the examiner, Scott does not teach or suggest co-administering an effective amount of an NO inhibiting or neutralizing agent to enhance the adjuvant effect of IL-12. In fact, Scott teaches nothing at all about such agent.

Fecho refers to a completely disparate topic than the vaccine compositions and methods of Scott, and adds nothing to Scott that suggests the presently claimed methods and compositions. Fecho clearly and repeatedly defines the purpose of its study:

> "The aim of the present study was to investigate the cellular and molecular mechanisms involved in the suppressive effect of *in vivo* administration of morphine to rats on the *in vitro* proliferative response of splenic lymphocytes to Con A stimulation." (page 5850, second col, under the heading "Discussion")

Fecho makes no reference to the use of NO inhibitors or neutralizing agents in the vaccine field at all. Fecho makes no suggestion that its NO inhibiting or neutralizing agents be combined with IL-12 for any reason. Thus, Fecho cannot provide a suggestion to combine NO inhibiting or neutralizing agents with IL-12 in order to provide a composition useful to adjuvant *any* vaccine antigen. In fact, the only mention of a cytokine in Fecho is the comment on page 5851, second paragraph:

> "For instance, IL-4, IL-10 and TGF-β synergistically inhibit IFN-γ-induced NO synthesis in murine macrophages....The interplay between cytokines in the induction and modulation of NO synthesis by macrophages is being investigated intensively by several laboratories and the findings of *future* studies promise to clarify this issue." (emphasis added).

No combination of IL-12 with NO inhibiting or neutralizing agents is suggested by either of the references, taken alone or together, for any reason, much less for increasing the adjuvanting ability of IL-12. It is the Applicants who made this inventive suggestion and supported it with enabling disclosure.

With respect, Applicants submit that the examiner is using hindsight to construct Applicants' invention by simply taking portions of one reference and piecing it into another reference, in the absence of any suggestion *in the prior art* to do so. Scott and Fecho taken together do not suggest the compositions and methods of this invention. While each of the cited references refers to components used in the presently claimed methods and compositions, there is no suggestion nor motivation to

combine the teachings of these references found within the references themselves. Such combination is not possible without hindsight.

The mere fact that the prior art may be modified in the manner suggested by the examiner does not make the modification obvious unless the prior art suggests the desirability of the modification.[1] The only source of the required motivation to make the adjuvant compositions of the invention and to use them in methods to enhance the immune response of vaccine antigens is provided by the Applicants' specification. As discussed above, the prior art references in combination and taken as a whole, do not suggest the claimed invention.

Applicants respectfully request that the examiner reconsider and withdraw this grounds for rejection of the claims.

In view of the above amendments and remarks, Applicants respectfully request that the examiner consider the amended claims and allow them to proceed to issuance in due course.

The Director is hereby authorized to charge any deficiency or credit any overpayment in any fee due with this paper to our deposit account number 08-3040.

Respectfully submitted,

HOWSON AND HOWSON
Attorneys for Applicant

By Mary E. Bak

Mary E. Bak
Registration No. 31,215
Spring House Corporate Center
Box 457
Spring House, PA 19477
(215) 540-9200

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1 *In re Fritsch*, 23 USPQ2d 1780, 1783-1784 (Fed. Cir. 1992), citing *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

VERSIONS WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Cancel claims 16-39 without prejudice as non-elected claims.

Amend claims 1, 40 and 41 as follows.

1(AMENDED). A method for enhancing the adjuvant effect of IL-12 comprising: co-administering to a mammalian patient said IL-12, a vaccine antigen, and an effective amount of at least one agent selected from the group consisting of a nitric oxide inhibiting agent and[/or] a neutralizing agent.

40(AMENDED). An adjuvant composition [suitable for use with a vaccine antigen] comprising an effective adjuvanting amount of IL-12 and an effective amount of at least one agent selected from the group consisting of a nitric oxide inhibiting agent and[/or] a neutralizing agent, in a pharmaceutically acceptable carrier.

41(AMENDED). A vaccine composition comprising an effective adjuvanting amount of IL-12, an effective amount of at least one agent selected from the group consisting of a nitric oxide inhibiting agent and[/or] a neutralizing agent, and an effective protective amount of a vaccine antigen in a pharmaceutically acceptable carrier.